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EXAMINER	
CELSA, BENNETT M	

ART UNIT	PAPER NUMBER
1639	47

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Please find below and/or attached an Office communication concerning this application or proceeding.

P.T. copy

Office Action Summary	Application No. 08/796,164	Applicant(s) Stamler et al.
	Examiner Bennett Celsa	Art Unit 1639

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *11, 12, 14-22, 27-29, 40, 41, 43, 44, 46, 63, 65, and 69-81* is/are pending in the application.

4a) Of the above, claim(s) *70, 71, and 73-80* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *11, 12, 14-22, 27-29, 40, 41, 43, 44, 46, 63, 65, 69, 72, and 81* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *35&44*
4) ☒ Interview Summary (PTO-413) Paper No(s). *33*
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission (e.g. amendment) filed on 10/31/2000 (paper no. 33) has been entered.

2. Applicant's supplemental amendment filed on 4/12/01 in paper no. 37 has been entered.

3. **NOTE**: Applicant's amendment in paper no. 33 added new claims 67-77, which pursuant to Rule 126 (previous claims 67-68 were previously canceled) were renumbered as claims 69-79, respectively. Similarly, new claims 78 and 79 (presented in paper no. 37) were similarly renumbered as claims 80 and 81.

Status Of The Claims

Claims 11-12, 14-22, 27-29, 40, 41, 43, 44, 46, 63, 65 and 69-~~79~~ 81 are currently pending.

Claims 11-12, 14-22, 27-29, 40, 41, 43, 44, 46, 63, 65, 69, 72 and 81 are under consideration.

Claims 70, 71, 73-80 are withdrawn from consideration as being directed to a nonelected invention.

4. Newly submitted claims 70-71 and 73-80 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: these claims are

directed to methods of making and methods of use whose methods possess different method objectives, utilize different compositional components and/or reaction conditions and are thus patentaly distinct and which additionlly require a different and separatetly burdensome manual/computer bibliographic search in patent and literature databases.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 70-71 and 73-80 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Withdrawn Objection(s) and/or Rejection (s)

Applicant's amendment and argument has overcome the new matter rejection of claims 63 and 65-66 found in the prior office action.

Applicant's amendment and argument has overcome the enablement rejection of claims 10-15, 46, 63, 65 and 66.

Applicant's arguments and amendment regarding the 102/103 rejection over the Wade and Castro reference was found persuasive.

Applicant's amendment has overcome the rejection of claims 24-26 under 35 U.S.C. 103(a) as being unpatentable over Feola et al. and Stamler, and if necessary further in view of Moore or Sharma.as applied to claims 17-19 and 26 above, and further in view of Chem. Res Tox. 1990 Vol. 3, pages 289-291.

Outstanding Objection(s) and/or Rejection (s)

5. Claims 16, 20-22, 27-28 and 40 are rejected under 35 U.S.C. 103(a) as obvious over Stamler et al, WO 93/09806 (5/93).

The Stamler refence teaches methods for "increasing blood oxygen transport by hemoglobin and myoglobin" which include the use of NO donating proteins including hemoglobin. E.g. see abstract.

Additionally, Stamler et al. teach that nitrosylated low molecular weight thiols (e.g. N-acetyl cysteine) serve as NO donating compounds (e.g. delivery of NO) which are therapeutically useful as smooth muscle relaxants, vasodilators and platelet inhibition (e.g. see abstract and pages 1-2 of Stamler).

Similarly to low molecular weight thiols, the Stamler reference further teaches that proteins (including hemoglobin), which are nitrosylated on oxygen, carbon or nitrogen sites possess the same therapeutic utility as nitrosylated/nitrated low molecular weight thiol compounds. (E.g. see page 6, lines 13-15; page 7, lines 17-21; page 58 describing nitrosylhemoglobin and claims).

The reference specifically discloses the use of nitrosylated proteins and low molecular weight nitrosating agents (e.g. see pages 1-2; page 24, lines 10-16) preparations thereof for the treatment of disorders by increasing oxygen capacity and transport; modulating CO and NO to tissues; scavenging radicals and vasodilation such as treating lung diseases (e.g. ARDS) and hypoxic disorders (E.g. see pages 19-25 and claims).

Further it is known in the art that hemoglobin is involved in regulating oxygen metabolism by its ability to bind reversibly to blood oxygen and thus facilitate the capability of blood to transport oxygen to bodily tissues (e.g. see bottom of page 19-top of page 20).

Accordingly, it would have been obvious to combine a low molecular weight thiol or nitrosothiol with either hemoglobin or nitrosated hemoglobin to deliver oxygen or NO (e.g. claim 16) since the Stamler reference teaches the use of the same compounds separately to effectuate the same function and in conjunction with hemoglobin to increase blood oxygen transport (e.g. see abstract).

Additionally, the use of Nitrosated/Nitrated proteins, including nitrosated/nitrated hemoglobin to deliver NO to tissues (e.g. claim 40) in order to effectuate the treatment of abnormalities or diseases which are mediated by nitric oxide and oxygen metabolism (e.g. lung disease, sickle cell anemia, heart disease, high blood pressure etc.) would have been obvious since the reference discloses the use of nitrosated proteins, including nitrosated hemoglobin, to treat such disease states.

6. Claim 41 is rejected under 35 U.S.C. 103(a) as being unpatentable over Stamler WO93 as applied to claims 16, 20-22, 27-28 and 40 above, and further in view of Moore et al., J.Biol.

Chem. Vol. 251, No. 9, (5/76) pages 2788-2794 or Sharma et al., J. Biol. Chem. Vol. 253, No. 18 (9/78) pages 6467-72.

The Stamler reference disclosure discussed in the above obviousness rejection over Stamler alone is hereby incorporated by reference in its entirety.

The Stamler reference although disclosing the use of nitrosyl-heme containing NO donors to deliver NO or its biological equivalent to tissues (e.g. present claim 40) fails to specifically disclose the use of nitrosylhemoglobin (e..g dependent claim 41).

However, nitrosylhemoglobin compositions are conventionally known in the art. E.g. See the Moore and Sharma references.

Additionally, the Stamler reference specifically addresses nitrosylhemoglobin on page 58.

One of ordinary skill in the art would be motivated to selected nitrosylhemoglobin to deliver NO to tissues in view of the Stamler reference which suggests that this compound would be expected to function as an NO-donating compound.

Accordingly, it would be obvious for one of ordinary skill in the art at the time of applicant's invention to select available nitrosylhemoglobin compositions to deliver NO as taught by Stamler.

Discussion

Applicant's arguments directed to the above obviousness rejections over the WO 93 alone and with Moore/Sharma were considered but deemed nonpersuasive for the following reasons.

Applicant first argues (e.g. regarding claim 16) that the reference fails to teach a method of making S-nitosylhemoglobin.

This argument is not persuasive since it's not commensurate to the presently claimed invetion which is not so limited.

Applicant argues that nitrosylhemoglobin (e.g. NO attached to heme) was thought to be useless until they discovered the inherent in vivo conversion of nitrosylhemoglobin to SNO-hemoglobin.

This argument is not persuasive since the reference teaches the use of nitrosylated hemoglobins which includes NO groups attached to "additional sites such as oxygen, carbon and nitrogen" and is not so limited to nitrosylhemoglobin; nor for that matter is applicant's claims limited to nitrosylhemoglobins. Additionally, even with respect to nitrosylhemoglobin, applicant's own argument has established that the use of this reference species would be reasonably expected to possess NO-donor capability due to its inherent conversion to S-nitrosylhemoglobin.

Applicant argues that the reference fails to teach the combination of hemoglobin with a low molecular weight (nitroso) thiol or nitrosated hemoglobin.

Applicant's argument is not persuasive since the reference clearly teaches the incorporation of NO donating compounds including low molecular weight (nitroso) thiols and

nitrosated hemoglobins in conjunction with the use of hemoglobin to increase oxygen transport. See e.g. the WO 93 abstract.

Applicant further argues that the reference fails to teach thiols as regulating oxygen metabolism and hemoglobin as being NO donating and thus no additive effects of combining these different compositional components.

This argument is not persuasive since compositional components are not always added together for purposes of additive properties. In the present instance the reference provides motivation to combine hemoglobins' blood oxygen transport properties with the complementary benefits imparted by an NO-donating protein.

With regard to claims 20-22, 27 and 28 applicant argues that the WO 93 reference fails to specifically address nitrosylhemoglobin.

Applicant's argument is not persuasive since applicant's arguments are not commensurate to the scope of the presently claimed inveniton which is not limited to nitrosylhemoglobin. Additionally, applicant's fails to appreciate the reference teaching as a whole in which the reference teaching of a nitrosylated/nitrosated hemoglobin genus would include nitrosylhemoglobin; which is in fact mentioned on page 58, lines 19-21 of WO 93/09806 as acknowledged by applicant.

With regard to claims 40 and 41 applicant argues that the Stamler WO 93/ document, failed to recognize the in vivo inherent mechanism of conversion of nitrosylhemoglobin to S-nitrosylhemoglobin .

This argument is not persuasive since the reference teaches nitrosylated hemoglobins which includes NO groups attached to "additional sites such as oxygen, carbon and nitrogen" which necessarily includes nitrosylhemoglobin (which is referenced by Stamler) ; and uses thereof within the scope of the present claims. In this respect, applicant's own argument has established that the use of this reference species in the manner suggested by the reference would be reasonably expected to possess NO-donor capability due to its inherent conversion to S-nitrosylhemoglobin.

Accordingly, the above obviousness rejections are hereby maintained.

7. Claims 10-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stamler (WO 93).

The presently claimed invention is directed to producing a composition comprising either SNO-Hb[FeII]O2 (produced in the presence of oxygen) or SNO-Hb[FeII] (produced in the absence of oxygen) by reacting "excess nitrosating agent" with purified hemoglobin (e.g. claims 10-11 and 13-14). Claims 12 and 15 specifically select a low molecular weight S-nitrosothiol as the nitrosating agent.

Stamler discloses different methods for thiol nitrosylation of proteins (as disclosed on page 30-31) which include:

1. reaction of nitrosylating agent (e.g. equimolar amounts of acidic NaNo2 as nitrosating agent in a buffered saline at pH 7.4 for tPA);

2. exposure of the protein (e.g. tPA to NO gas in buffered saline)

With regard to the above, Stamler further notes that other oxides of nitrogen can be utilized (e.g. NOCL, N2O3) as well as other nitroso equivalents.

However, the above two reference methods for thiol nitrosylation fail to disclose the use of "excess" nitrosating agent, and preferably the selection of a low molecular weight S-nitrosothiol as the nitrosating agent for thionitrosylation of hemoglobin.

But the Stamler reference (e.g. Example 19 on pages 58-59) specifically discloses the preferential selection of a low molecular weight S-nitrosothiol (e.g. SNOAC) instead of acidic Na NO2 as utilized for tPA due to reduced ability of the SNOAC as compared with acidic nitrate to bind at the redox metal which reduces oxygen binding affinity.

Further, the use of "excess nitrosating agent" in either reaction 1. or 2 above is suggested by the Stamler reference since providing a greater concentration of NO serves to enhance the therapeutic efficacy of the nitrosylated proteins (e.g. see bottom of page 23-top of 24)

It is further noted that the use of higher pH values (e.g. pH 7.4) than that utilized in the thionitrosylated hemoglobin example (e.g. pH 6.9 Example 19) is also suggested by the reference since thionitrosylated proteins are known to be stable under physiological conditions (e.g. TBS, pH 7.4, room temperature: see page 31) and further the reference discloses the use of pH7.4 in the the making and storage of vaious thiol proteins. Additionally, the thiol-protein synthetic steps are analogous to that of Example 19: see page 30, lines 20-27; page 33, lines 20-26). Optimization of reaction conditions, including pH, is within the skill of the art.

Additionally, it is a matter of obvious design choice to select anaerobic conditions for making a deoxygenated hemoglobin derivative and aerobic conditions when desiring to make an oxygenated hemoglobin derivative.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to synthesize thionitrosylated hemoglobin by using "excess" nitrosating agent, and preferably a low molecular weight S-nitrosothiol, and to further optimize pH during nitrosylation to utilize physiological conditions to form a more stable nitrosylated oxy/deoxy hemoglobin.

Discussion

Applicant's arguments directed to the above obviousness rejection were considered but deemed nonpersuasive for the following reasons.

Applicant argues that the reference example for making S-nitrosylated hemoglobin (e.g. Example 19) teaches using pH of 6.9 and the reference fails to exemplify the making of S-nitrosylated hemoglobin at pH of 7.4 or higher.

This argument is not persuasive since the rejection above is raised under obviousness and not anticipation.

Applicant argues that stability of SNO-tPA at pH 7.4 does not reveal anything about the reaction conditions under which it can be made ; and applicant further argues that the reaction conditions for making SNO-tPA are not analogous to those conditions for making S-nitrosylated hemoglobin in Example 19.

This argument was considered but deemed nonpersuasive for the following reasons.

Applicant's argument fails to consider the Stamler reference teaching as a whole which address both the syntheses of S-nitrosylated proteins other than hemoglobin (e.g. tPA, BSA etc) and storage of the resulting thiol proteins at pH 7.4 as well as the stability of the SNO bonds of these proteins under physiologic conditions at pH 7.4. Accordingly, the reference provides ample motivation for one of ordinary skill in the art to optimize pH to pH 7.4 in light of the reference teaching.

Accordingly, the above obviousness rejection is maintained.

8. Claims 17-19, 29, 69, 72 and 81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Feola et al. , U. S. Pat. No. 5,439,882 (8/95: filed 5/93 or earlier) and Stamler, and if necessary further in view of Moore or Sharma.

Feola et al. disclose the state of the prior art regarding "blood substitutes" as being an emergency resuscitative fluid that:

a. Restores blood volume;

b. Transports oxygen;

c. Reduces vasoconstiction. See Feola col. 1.

Feola et al. disclose the use of "blood substitutes" which comprises hemoglobin alone or combined with glutathione as a blood substitute to treat blood disorders (e.g. sickle cell anemia) (e.g. see Abstract, examples and columns 1 and 7).

The Feola reference "blood substitute" composition and intended use thereof (e.g. treat sickle cell anemia) differs from the presently claimed invention which utilizes nitrosated hemoglobin alone or with a low molecular weight S-nitrosothiol instead of hemoglobin or hemoglobin combined with glutathione.

However, Stamler et al. teach that nitrosylated low molecular weight thiols (e.g. N-acetyl cysteine) serve as NO donating compounds (e.g. delivery of NO) which are therapeutically useful as smooth muscle relaxants, **vasodilators** and platelet inhibition (e.g. see abstract and pages 1-2 of Stamler).

The Stamler reference specifically discloses the use of nitrosylated proteins and low molecular weight nitrosating agents (e.g. see pages 1-2; page 24, lines 10-16) preparations thereof for the treatment of disorders by increasing oxygen capacity and transport; modulating CO and NO to tissues; scavenging radicals and vasodilation such as treating lung diseases (e.g. ARDS) and hypoxic disorders (E.g. see pages 19-25 and claims).

Thus, the Stamler et al. reference provides the skilled artisan with motivation to utilize nitrosated hemoglobin alone or with a low molecular weight S-nitrosothiol to make a blood substitute for treating sickle cell anemia in order to increase blood volume, oxygen delivery and reduce vasoconstriction as effected by nitrosated hemoglobins alone or in conjunction with a nitrosothiol.

Further, nitrosylated hemoglobin preparations, e.g. nitrosylhemoglobin compositions, are conventionally known in the art. E.g. See the Moore and Sharma references.

Accordingly, it would have been obvious to the skilled artisan at the time of applicant's invention to make a blood substitute comprising nitrosated hemoglobin alone or in conjunction with a low molecular weight nitrosothiol for their expected benefits as suggested by the Stamler reference and in analogous manner as the Feola reference composition..

Discussion

Applicant's arguments directed to the above obviousness rejection were considered but deemed nonpersuasive for the following reasons.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Arguments presented against the Stamler reference already addressed by the Examiner in previous obviousness rejections over this reference (e.g. arguments not commensurate etc.) are specifically incorporated by reference in their entirety and not included here.

Applicant argues that their present specification (e.g. pages 17, 19, 57, 58 etc) teaches that S-nitrosylated hemoglobin can be a vasoconstrictor in some cases.

This argument is not persuasive since it is not commensurate to the presently claimed inveniton; which is not limited to S-nitrosylhemoglobin nor conditions required for vasodilation activity of any nitrosylated/nitrosated hemoglobin compounds.

Double Patenting

9. Claims 11-12, 14-22, 27-29, 40, 41, 43, 44, 46, 63, 65, 69, 72 and 81 of this application conflict with claims which are present in Application No.08/667,003 and 08/796,164. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

New Objection (s) and/or Rejection (s)

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.
>
> (f) he did not himself invent the subject matter sought to be patented.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was

not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 69 and 72 are rejected under 35 U.S.C. 102(e,f) as being anticipated by, or alternatively under 35 USC 103 as being obvious over Stamler et al. US Pat. No. U.S. Patent No. 6,291,424 (9/18/01: filed March 1995 or earlier). The Stamler patent discloses and claims compositions comprising a narrow genus of S nitrosated/nitrosylated heme proteins which include hemoglobin within the scope of the presently claimed invention. Deoxy- hemoglobins are within the scope of the disclosed/patented invention (as immediately envisaged) or alternatively represents an obvious variant thereof of oxy-hemoglobins

13. Claims 21, 22, 27, 28, 40, 41, 69 and 72 are rejected under 35 U.S.C. 102(e,f) as being anticipated by, or alternatively under 35 USC 103 as being obvious over Stamler et al. US Pat. No. 6,583,113 (6/03: filed 3/95 or earlier).

Stamler et al teaches (claims and discloses)compositions comprising nitrosylated heme proteins (including (S) nitrosated/nitrosylate hemoglobin) and the use thereof to deliver NO to tissues for the prevention/treatment of various diseases/disorders including cardiovascular diseases/disorders (e.g. ARDS, heart disease etc.) . See e.g. col .1-2 ; col. 4; col. 5; col. 9-12; examples; patent claims. Deoxy- hemoglobins are within the scope of the disclosed/patented invention (as immediately envisaged) or alternatively represents an obvious variant thereof of oxy-hemoglobins.

14. Claims 16-22, 27- 29, 40, 41, 69, 72 and 81 are rejected under 35 U.S.C. 102(e,f) as being anticipated, or alternatively under 35 USC 103 as being obvious over Stamler et al. US Pat. No. 6,471,978 (10/02: filed 6/2/95 or earlier).

Stamler et al. teach compositions that comprise nitric oxide (NO adducts) (e.g upon administration), including S-nitrosothiols (e.g. upon administration or formed in vivo upon NO adduct administration) cause vasodilation and platelet inhibition (e.g. see col 1) which prevents thrombus formation (e.g. see col. 2). Accordingly, the reference teaches that an administered "nitric oxide adduct" (e.g. a compound or a device comprising a compound: see col. 4) treats damaged vasculature which are susceptible to thrombus formation (e.g see col. 3). The selection of "nitric oxide adducts" of hemoglobin (e.g. (S) nitrosated/nitrated/polynitrosated) is anticipated or in the alternative obvious since hemoglobin is a preferred (e.g. claimed embodiment) "nitric oxide adduct" ie. includes nitrosohemeproteins, with hemoglobin being preferred. Eg. See patent claims 1, 18-24; 30, 36-42,48, and 54-60); *In re Schaumann*, 572 F.2d

312. 197 USPQ 5 (CCPA 1978). Additionally, the reference teaches combination of S-nitrosothiols with hemoglobin for their expected NO donating properties thus anticipating or rendering obvious present claims directed to "potentiation of NO delivery". The reference teaching of compositions comprising nitrosated/nitrosylated hemoglobins and/or low MW S-nitrosothiols for administration would inherently, upon administration, produce the scavenging of oxygen free radicals as reduced blood pressure (E.g. vasodilatory effect).. E.g. The prior art procedure inherently meets claim limitations because the same protein is applied in the same way in the same amount. *In re Best*, 195 USPQ 430,433 (CCPA 1977); *Ex parte Novitski*, 26 USPQ2d 1389 (B.P.A.I, 1993). Further, the reference discloses the treatment of damaged blood vessels as well as the prevention/treating of cardivasular/respiratory diseases (e.g. heart disease and ARDS) . See claims and col. 1-4; patent claims. Deoxy- hemoglobins are within the scope of the disclosed/patented invention (as immediately envisaged) or alternatively represents an obvious variant thereof of oxy-hemoglobins.

15. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

16. Claims 69 and 72 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,291,424 (9/18/01: filed March 1995 or earlier). Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent claims are directed to compositions comprising a narrow genus of S nitrosated/nitrosylated heme proteins which include hemoglobin within the scope of the presently claimed inveniton. Deoxy- hemoglobins are within the scope of the disclosed/patented invention (as immediately envisaged) or alternatively represents an obvious variant thereof of oxy-hemoglobins.

17. Claims 69 and 72 provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of copending Application No. 09/835,038 (PG PUB US 2002/0052314A1 May 2, 2002). Although the conflicting claims are not identical, they are not patentably distinct from each other because the application claims compositions comprising S- nitrosated/nitrosylated hemoglobin which comprise a small number of deoxy- and oxy- (which are obvious variants or each other) hemoglobin species

(e.g. 4 species deoxy/oxy nitrosated/nitroyslated Hb) which would include S-nitrosylated hemoglobins). Deoxy- hemoglobins are within the scope of the disclosed/patented invention (as immediately envisaged) or alternatively represents an obvious variant thereof of oxy-hemoglobins.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

18. Claims 19-22, 27-28, 40-41, 69 and 72 provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-17 (especially claims 7-9 and 17) of copending Application No. 10/216,865 (PG PUB US 2003/0079674A1 Jan 9, 2003). Although the conflicting claims are not identical, they are not patentably distinct from each other because the application claims compositions comprising S- nitroso hemoglobins and uses thereof which comprise NO delivery, including treating/preventing cardiovascular/respiratory disorders (e.g. Heart disease, ARDS etc: see patent claim 9 interpreted in light of disclosure: e.g. at page 6) . Deoxy- hemoglobins are within the scope of the disclosed/patented invention (as immediately envisaged) or alternatively represents an obvious variant thereof of oxy-hemoglobins. The adminsitration of hemoglobins to patients for the treatment of cv/pulmonary disorders would inherently result in the scavenging of oxygen free radicals and/or the reduction of blood pressure (e.g. vasodilatory effect).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

19. Claims 21, 22, 27, 28, 40, 41, 69 and 72 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,583,113 (6/03). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims teach compositions comprising nitrosated/nitrosylated heme proteins (e.g.including S-nitrosylated hemoglobins : see cliams 1-3) and their use (E.g. delivery of NO to tissues via administration) in treaing/preveinting diseases including cardiovascular diseases such as ARDS (E.g. see claims 1 and 4:col. 11-12) and heart disease. Deoxy- hemoglobins are within the scope of the disclosed/patented invention (as immediately envisaged) or alternatively represents an obvious variant thereof of oxy-hemoglobins.

20. Claims 16-22, 27- 29, 40, 41, 69, 72 and 81 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-65 of Stamler et al. US Pat. No. 6,471,978 (10/02: filed 6/2/95 or earlier) as interpreted in light of the specification regarding the scope of treatment of vasculature damage and inherency.

Stamler et al. teach (e.g. disclose and claim) compositions that comprise nitric oxide (NO adducts) (e.g upon administration), including S-nitrosothiols (e.g. upon administration or formed in vivo upon NO adduct administration) cause vasodilation and platelet inhibition (e.g. see col 1) which prevents thrombus formation (e.g. see col. 2). Accordingly, the reference teaches that an administered "nitric oxide adduct" (e.g. a compound or a device comprising a compound: see col. 4) treats damaged vasculature which are susceptible to thrombus formation (e.g see col. 3). The

selection of "nitric oxide adducts" of hemoglobin (e.g. (S) nitrosated/nitrated/polynitrosated) is anticipated or in the alternative obvious since hemoglobin is a preferred (e.g. claimed embodiment) "nitric oxide adduct" ie. includes nitrosohemeproteins, with hemoglobin being preferred. Eg. See patent claims 1, 18-24; 30, 36-42,48, and 54-60); *In re Schaumann*, 572 F.2d 312. 197 USPQ 5 (CCPA 1978). Additionally, the reference teaches combination of S-nitrosothiols with hemoglobin for their expected NO donating properties thus anticipating or rendering obvious present claims directed to "potentiation of NO delivery". The reference teaching of compositions comprising nitrosated/nitrosylated hemoglobins and/or low MW S-nitrosothiols for administration would inherently, upon administration, produce the scavenging of oxygen free radicals as reduced blood pressure (E.g. vasodilatory effect).. E.g. The prior art procedure inherently meets claim limitations because the same protein is applied in the same way in the same amount. *In re Best*, 195 USPQ 430,433 (CCPA 1977); *Ex parte Novitski*, 26 USPQ2d 1389 (B.P.A.I, 1993). Further, the reference discloses the treatment of damaged blood vessels as well as the prevention/treating of cardivasular/respiratory diseases (e.g. heart disease and ARDS) . See claims and col. 1-4; patent claims. Deoxy- hemoglobins are within the scope of the disclosed/patented invention (as immediately envisaged) or alternatively represents an obvious variant thereof of oxy-hemoglobins.

General information regarding further correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Celsa whose telephone number is (703) 305-7556.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew J. Wang (art unit 1639), can be reached at (703)306-3217.

Any inquiry of a general nature, or relating to the status of this application, should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Bennett Celsa (art unit 1639)

October 20, 2003

BENNETT CELSA
PRIMARY EXAMINER